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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/693,059	10/23/2003	James McSwiggen	03-465-A (400.136)	1557

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EXAMINER	
PITRAK, JENNIFER S	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,059	MCSWIGGEN ET AL.	
	Examiner	Art Unit	
	JENNIFER PITRAK	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18 and 20-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18 and 20-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/09/2007; 10/04/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the species indicated in the reply filed on 04/08/2008 is acknowledged. The traversal is on the ground(s) that search of each species is not an undue search burden. This is found persuasive and the requirement for an election of species is withdrawn.

Applicants amended claims 18 and 20-33 and cancelled claim 19. Claims 18 and 20-33 are currently pending and are under examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 18 and 20-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Fosnaugh and McSwiggen (US2003/0143732, filed as provisional application number 60/315,315 on 08/28/2001, of record, 10/04/2007 IDS).

The applied reference has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing

under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The instant claims are to a chemically modified double stranded nucleic acid (dsNA) molecule comprising one or more ribonucleotides wherein each strand is 19-29 nucleotides in length and either or both strands comprise two or more modifications wherein at least two modifications are different from each other and are selected from the group consisting of LNA, 2'-methoxy-ethoxy (2'-MOE), 2'-methyl-thio-ethyl, 2'-F, 2'-Cl, 2'-azido, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluromethoxy-ethoxy, 4'-thio, and 2'-O-methyl modifications. The claims are further to the dsNA molecule having an inverted deoxy abasic moiety at the 5'-end, 3'-end, or both the 5'- and 3'-ends or the sense strand and an inverted deoxy abasic moiety at the 3'-end of the antisense strand. The claims are also to the siNA molecule wherein any of the pyrimidine nucleotides in the sense strand are 2'-O-methyl-modified, any of the purine nucleotides in the sense strand are 2'-deoxy-modified, any of the pyrimidine nucleotides in the sense strand are 2'-F-modified, any of the pyrimidine nucleotides in the antisense strand are 2'-F-modified, or any of the purine nucleotides in the antisense strand are 2'-O-methyl-modified. Claim 33 specifies the dsNA of claim 18 in a pharmaceutically acceptable carrier or diluent. It is noted that the reference in the instant claims refer to "sense" and "antisense" strands of the dsNA molecule is interpreted strictly as useful for distinguishing between the two strands of the dsNA, because the specification indicates that both strands can be complementary to a target molecule.

Fosnaugh and McSwiggen teach 21-nucleotide siRNA duplexes useful for treating asthma (p.1, paragraph 6; p.3, paragraph 13). The siRNAs comprise one or more 2'-O-methyl-modified pyrimidines (uracil, cytosine, or thymine) in the sense strand and a terminal cap moiety at the 3'-end, 5'-end, or both the 3'- and the 5'-end (Figure 5C; p.3, paragraph 18; p.5, paragraphs 40-41). The terminal cap moieties are deoxy abasic moieties and can also be present at the 3'-end of the antisense strand (p.9, paragraph 65; Figures 4C and 5C). Fosnaugh and McSwiggen further teach siRNAs wherein the antisense strand has one or more 2'-F-modified pyrimidines (Figure 5); siRNAs wherein the sense strand has 2'-deoxy-modified purines or 2'-F-modified pyrimidines (paragraphs 39-41; Figure 5); or siRNAs wherein the antisense strand has 2'-O-methyl-modified purines (paragraphs 39-41; Figure 5). At paragraphs 7 and 66 (pages 1 and 9), Fosnaugh and McSwiggen teach that LNAs can be incorporated into siRNAs. Thus, Fosnaugh and McSwiggen clearly anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18 and 20-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir, *et al.* (2001, EMBO J., v.20(23):6877-88, of record, 07/09/2007 IDS), Monia and Cowsert (2000, U.S. Patent 6,033,910), Piekin (1991, Science, v.253:314-7, of record,

07/09/2007 IDS), and Matulic-Adamic, *et al.* (1999, U.S. Patent 5,998,203, of record, 07/09/2007 IDS).

The claims are to a chemically modified dsNA molecule as described above.

Elbashir, *et al.* teach siRNAs that are 21-22 nucleotides in length and that are formulated with pharmaceutically acceptable carriers (water or buffer after gel purification) (p.6886, "RNA preparation and RNAi assay"). Elbashir, *et al.* teach the incorporation of 2'-deoxy-nucleotides in one or both strands of the siRNA and the incorporation of 2'-O-methyl-nucleotides in one or both strands of the siRNA (Figure 4). Elbashir, *et al.* do not teach all of the instantly claimed modifications and does not teach siRNAs having terminal cap moieties.

At the time of filing of the instant application, it was well known that antisense oligonucleotides were useful for downregulating gene expression and that such molecules are preferably modified in their sugar-phosphate backbone for the purpose of increasing stability and resistance to cellular nucleases. Monia and Cowsert represent the state of the antisense art at the time of filing of the instant application. They describe antisense oligonucleotides as comprised of RNA or DNA (2'-deoxy) or mimetics thereof and that such nucleotides have non-naturally-occurring nucleobases, sugars and covalent internucleoside linkages, which are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for the target nucleic acid, and increased resistance to nucleases (column 6, lines 4-25). The modified oligonucleotides may contain one or more substituted sugar moieties, preferably those listed in column 8, which include 2'-F, 2'-Cl, 2'-CF_3, and 2'-MOE modifications. Example 5 in column 34 describes a "gapmer", which has both 2'-methyl and 2'-deoxy modifications in a single antisense oligonucleotide. Such modifications are incorporated into the antisense

oligonucleotides of Monia and Cowsert without regard to sequence, indicating that both modified purines and modified pyrimidines are equally beneficial for enhancing the stability of the oligonucleotides.

Pieken, *et al.* teach that incorporation of 2'-F modifications in pyrimidines (C and U) stabilized ribozymes from degradation in rabbit serum (abstract).

Matulic-Adamic, *et al.* teach oligonucleotides having 5'- and 3'- terminal cap moieties and that such cap moieties protect the molecules from nucleases. The cap moieties are described as including inverted abasic moieties (columns 3 and 4).

It would have been obvious to one of skill in the art to make siRNAs having 2'-modified nucleotides as taught by Elbashir, et al. and to include the modifications used for stabilizing antisense oligonucleotides and ribozymes, as taught by Monia, *et al.*, Pieken, *et al.*, and Matulic-Adamic, *et al.* It further would have been obvious to make siRNAs with individual strands that are either partially modified or that are modified with more than one type of modification, and particularly with 2'-F pyrimidines as taught by Pieken, *et al.* Elbashir, *et al.* demonstrated that siRNAs with partial modification (2'-deoxy nucleotides at the ends of siRNA strands) inhibited target gene expression as well as did non-modified siRNAs and that fully 2'-deoxy- or 2'-methyl-modified siRNAs were less effective at silencing than the partially modified or unmodified siRNAs. Monia, *et al.* demonstrated antisense inhibition using gapmers having two types of modifications within one strand. Monia demonstrated that the modifications were effective when used on either purines or pyrimidines. Pieken, demonstrated that ribozymes containing 2'-F-modified cytidines and uridines were stabilized against degradation and Matulic-Adamic, *et al.* taught that oligonucleotides can be stabilized with terminal cap moieties. Using

the oligonucleotide modifications that were well known to provide increased stability to siRNAs would have been to one of skill in the art to incorporate into siRNAs for the same purpose. One would reasonably expect such modifications to improve stability of siRNAs and the particular arrangement of such modifications would be well within the abilities of one skilled in the art to determine by no more than routine experimentation and optimization.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER PITRAK whose telephone number is (571)270-3061. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak, PhD
Examiner
Art Unit 1635

/Tracy Vivlemore/
Primary Examiner, Art Unit 1635